Important Efficacy and Safety Information for Healthcare Professionals

RoActemra® (tocilizumab) intravenous (IV) infusion for Systemic Juvenile Idiopathic Arthritis (sJIA) and Polyarticular Juvenile Idiopathic Arthritis (pJIA)

This educational material is provided by Roche Products Ltd is mandatory as a condition of the Marketing Authorisation in order to minimise important selected risks

Full prescribing information can be found in the RoActemra Summary of Product Characteristics (SmPC) via the electronic Medicines Compendium (eMC) website: www.medicines.org.uk

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Indication and usage for patients with sJIA and pJIA

sJIA

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to methotrexate [MTX] or where treatment with MTX is inappropriate) or in combination with MTX.[1]

The efficacy of RoActemra for the treatment of active sJIA was assessed in a 12 week Phase III, randomised, double-blind, placebo-controlled, parallel-group, two-arm study.[1]

pJIA

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.[1]

The efficacy of RoActemra for the treatment of active pJIA was assessed in a three-part study. Part I consisted of a 16-week active RoActemra treatment lead-in period, followed by Part II, a 24-week randomised double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period.[1]

Patient counselling information and laboratory monitoring

Patient counselling information

Before initiating therapy, patients and parents/guardians of sJIA and pJIA patients should be advised of the potential risks and benefits of RoActemra.

The potential risks associated with RoActemra treatment

- Infections:

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. Inform patients and parents/guardians of sJIA and pJIA patients that RoActemra may lower the patient's resistance to infections.[1]

Instruct the patient and their parents/guardians to seek immediate medical attention if signs or symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment. Signs or symptoms of infection may include:[1]

- Fever
- Persistent cough
- Weight loss
- Throat pain or soreness
- Wheezing
- Red or swollen skin blisters, skin tears or wounds
- Severe weakness or tiredness

- Hypersensitivity reactions:[1]

Inform the patient and parents/guardians of sJIA and pJIA patients that serious allergic reactions including anaphylaxis have been reported in association with RoActemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced allergic reactions during previous treatment with RoActemra. Most allergic reactions occur during infusion or within 24 hours of RoActemra administration, although allergic reactions can occur at any time. Fatal anaphylaxis has been reported after marketing authorisation during treatment with RoActemra.

Instruct the patient and their parents/guardians to seek immediate medical attention if signs or symptoms suggesting a systemic allergic reaction appear in order to ensure rapid evaluation and appropriate treatment. Possible signs or symptoms of a systemic allergic reaction include:

- Rash, itching or hives
- Chest pain
- Feeling dizzy or faint
- Hypotension
- Shortness of breath or trouble breathing
- Swelling of the lips, tongue or face
- Severe stomach pain or vomiting

During the infusion, watch the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately, appropriate therapy initiated and RoActemra permanently discontinued.

- Vaccinations:[1]

Inform patients and parents/guardians of sJIA and pJIA patients that any live or live-attenuated vaccines should not be received during RoActemra therapy. Patients should be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Before you administer RoActemra, ask the patient or parents/guardians of sJIA and pJIA patients if the patient:[1]

- Has an infection, is being treated for an infection or has a history of recurring infections
- Has signs of an infection, such as a fever, cough or headache, or is feeling unwell
- Has herpes zoster or any other skin infection with open sores
- Has had any allergic reactions to previous medications, including RoActemra
- Is a young woman of childbearing age and may be pregnant or sexually active. Female patients of childbearing potential must use effective contraception during (and up to 3 months after) treatment. RoActemra should not be used during pregnancy unless clearly necessary
- Has diabetes or other underlying conditions that may predispose him or her to infection
- Has tuberculosis (TB), or has been in close contact with someone who has had TB
  - As recommended for other biological treatments, sJIA/pJIA patients should be screened for latent TB infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra
- Is taking other biological drugs to treat sJIA/pJIA, or receiving atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin or benzodiazepines
- Has had or currently has viral hepatitis or another hepatic disease
- Has a history of gastrointestinal ulcers or diverticulitis
- Has recently received a vaccination or are scheduled for any vaccination
- Has cancer, cardiovascular risk factors, such as raised blood pressure and raised cholesterol levels, or moderate to severe kidney function problems
- Has a history of macrophage activation syndrome (MAS) (Only relevant to sJIA patients)

Laboratory monitoring[1]

Alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, neutrophils and platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (see section Warning and Precautions, Laboratory parameters).

Clinical response[1]

The demonstrated efficacy associated with RoActemra treatment

Demonstrated efficacy associated with RoActemra treatment in pJIA

In the CHERISH study, 48.1% (39/81) of placebo-treated patients and 25.6% (21/82) of RoActemra-treated patients had a JIA ACR30 flare by Week 40 relative to Week 16 (primary endpoint). These proportions were statistically significantly different (p=0.0024).

The percentages of patients achieving JIA ACR30, 50 and 70 responses are shown below.

CHERISH: JIA ACR response rates at Week 40 relative to baseline (percentage of patients)

Response rate	RoActemra n=82	Placebo n=81
JIA ACR30	74.4%*	54.3%*
JIA ACR50	73.2%*	51.9%*
JIA ACR70	64.6%*	42.0%*

*$p<0.01$, RoActemra vs. placebo

The number of active joints was significantly reduced compared with baseline in patients receiving RoActemra compared with placebo (p=0.0435), as was the physician's global assessment of disease activity (p=0.0031).

The adjusted mean change in the pain visual analogue scale (VAS) after 40 weeks of RoActemra treatment was 32.4 mm on a 0–100 mm scale compared with a reduction of 22.3 mm for placebo patients. This greater reduction in pain on RoActemra in comparison with placebo (highly statistically significant (p=0.0076)).

Demonstrated efficacy associated with RoActemra treatment in sJIA

Phase III study - The TENDER study

In the TENDER study, 85% (64/75) of RoActemra-treated patients and 24% (9/37) of placebo-treated patients achieved the primary endpoint of at least 30% improvement in the JIA ACR core set (JIA ACR30 response) and absence of fever (no temperature recording ≥37.5°C in the preceding 7 days) at Week 12. These proportions were highly significantly different (p<0.0001).

The percentages of patients achieving JIA ACR30, 50, 70 and 90 responses are shown below. Responses are maintained in the ongoing open-label extension phase.

TENDER: JIA ACR response rates at Week 12 (% patients)

Response rate	RoActemra n=75	Placebo n=37
JIA ACR30	90.7%*	24.3%
JIA ACR50	85.3%*	10.8%
JIA ACR70	70.7%*	8.1%
JIA ACR90	37.3%*	5.4%

*$p<0.0001$, RoActemra vs. placebo

Systemic effects

In the RoActemra-treated patients, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥37.5°C in the preceding 14 days) at Week 12 versus only 21% of placebo-treated patients (p<0.0001).

The adjusted mean change in the pain visual analogue scale (VAS) after 12 weeks of RoActemra treatment was a reduction of 41 points on a scale of 0–100 compared to a reduction of 1 for placebo-treated patients (p<0.0001).

Corticosteroid tapering

Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) RoActemra-treated patients versus one (3%) placebo-treated patient were able to reduce their corticosteroid dose by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12 (p=0.028). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids at Week 44, while maintaining JIA ACR responses.

Health-related and quality-of-life outcomes

At Week 12, the proportion of RoActemra-treated patients showing a minimally clinically important improvement in the Childhood Health Assessment Questionnaire – Disability Index (defined as an individual total score decrease of ≥0.13) was significantly higher than in placebo-treated patients, 77% versus 19% (p<0.0001).

Laboratory parameters

In the RoActemra-treated patients, 67% (50/75) had a haemoglobin less than the lower limit of normal (LLN) at baseline and 80% (40/50) of these patients had an increase in their haemoglobin to within the normal range at Week 12, in comparison to only 7% (2/29) of placebo-treated patients with haemoglobin <LLN at baseline (p<0.0001).

Warnings and precautions

Infections[1]

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. RoActemra treatment should not be initiated in patients with active infections. Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for active sJIA and pJIA, as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute-phase reaction. The effects of RoActemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (including younger children with sJIA and pJIA who may be less able to communicate their symptoms) and parents/guardians should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Tuberculosis[1]

As recommended for other biological treatments, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a TB infection occur during or after therapy with RoActemra.

Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with RoActemra, patients who screened positive for hepatitis were excluded.[1]

Complications of diverticulitis

RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.[1]

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported in association with infusion of RoActemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with RoActemra. If an anaphylactic reaction or other serious hypersensitivity/serious infusion-related reaction occurs, administration of RoActemra should be stopped immediately and RoActemra should be permanently discontinued. Fatal anaphylaxis has been reported during treatment with RoActemra.[1]

Active hepatic disease and hepatic impairment

Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases; therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment. RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.[1]

Laboratory parameters

Neutrophils[1]

Decreases in neutrophil counts have occurred following treatment with RoActemra. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections. Infections have been reported in neutropenic patients.

Neutrophils should be monitored at the time of second infusion and thereafter according to good clinical practice.

Low absolute neutrophil count (ANC)[1]

Laboratory value (cells x 10^9/L)	Action
ANC >1	Maintain RoActemra dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to >1 x 10^9/l resume RoActemra
ANC <0.5	Discontinue RoActemra The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient

Platelets[1]

Decreases in platelet counts have occurred following treatment with RoActemra.

Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/µl). In patients who develop a platelet count <50 x 10^3/µl, continued treatment is not recommended.

Platelets should be monitored at the time of second infusion and thereafter according to good clinical practice.

Low platelet count[1]

Laboratory value (cells x 10^3/µL)	Action
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing When platelet count is >100 x 10^3/µl resume RoActemra
<50	Discontinue RoActemra The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient

Hepatic transaminases[1]

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN). In patients with baseline ALT or AST >5 x ULN, treatment is not recommended.

ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice.

ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.

Liver enzyme abnormalities[1]	
Laboratory value	**Action**
>1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until ALT/AST have normalised
>3 to 5 x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN
>5 x ULN	Discontinue RoActemra The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient

Lipids[1]

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with RoActemra.

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders[1]

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy[1]

Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations[1]

Live and live-attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. It is recommended that sJIA and pJIA patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk in RA patients[1]

Patients with sJIA/pJIA should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

Combination with TNF antagonists[1]

There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA/pJIA patients. RoActemra is not recommended for use with other biological agents.

Macrophage activation syndrome (MAS)[1]

MAS is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, RoActemra has not been studied in patients during an episode of active MAS.

Undesirable effects[1]

In general, the adverse drug reactions in sJIA patients were similar in type to those seen in RA patients.

sJIA

Infections[1]

In the 12-week controlled clinical study, the rate of all infections in the RoActemra group was 344.7 per 100 patient-years compared with 287.0 per 100 patient-years in the placebo group. In the ongoing open-label extension study, the overall rate of infections remained similar at 306.6 per 100 patient-years.

In the 12-week controlled clinical study, the rate of serious infections in the RoActemra group was 11.5 per 100 patient-years. At 1 year in the ongoing open-label extension study, the overall rate of serious infections remained stable at 11.3 per 100 patient-years.

Infusion reactions[1]

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled clinical study, 4% of patients from the RoActemra group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the RoActemra group, 16% of patients experienced an event within 24 hours of infusion compared to 5.4% of patients in the placebo group during the 12-week clinical study. In the RoActemra group, the events included, but were not limited to, rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with RoActemra and requiring treatment discontinuation were reported in <1% (1 out of 112) patients treated with RoActemra during the controlled and open-label clinical study.

Immunogenicity[1]

All 112 patients were tested for anti-RoActemra antibodies at baseline. Two patients developed positive anti-RoActemra antibodies, with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-RoActemra antibody formation might be underestimated because of interference of RoActemra with the assay and higher drug concentration observed in children compared to adults.

Neutrophils[1]

During routine laboratory monitoring in the 12-week clinical study, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the RoActemra group, and no decreases in the placebo group.

In the ongoing open-label clinical study, decreases in neutrophil counts below 1 x 10^9/l occurred in 15% of the RoActemra group.

Platelets[1]

During routine laboratory monitoring in the 12-week clinical study, 3% of patients in the placebo group and 1% in the RoActemra group had a decrease in platelet count to ≤100 x 10^3/µl.

In the ongoing open-label clinical study, decreases in platelet counts below 100 x 10^3/µl occurred in 3% of patients in the RoActemra group, without associated bleeding events.

Hepatic transaminase elevations[1]

During routine laboratory monitoring in the 12-week clinical study, elevation in ALT or AST ≥3 x ULN occurred in 5% and 3% of patients, respectively, in the RoActemra group, and none in the placebo group.

In the ongoing open-label clinical study, elevation in ALT or AST ≥3 x ULN occurred in 12% and 4% of patients, respectively, in the RoActemra group.

Immunoglobulin G[1]

IgG levels decrease during therapy. A decrease to the LLN occurred in 15 patients at some point in the study.

Lipid parameters[1]

During routine laboratory monitoring in the 12-week clinical study, elevation in total cholesterol >1.5 x ULN to 2 x ULN occurred in 1.5% of the RoActemra group and none in the placebo group. Elevation in LDL >1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the RoActemra group, and none in the placebo group.

Undesirable effects[1]

In general, the adverse drug reactions in pJIA patients were similar in type to those seen in RA patients.

pJIA

Infections[1]

Following 184.4 patient-years of exposure with RoActemra in pJIA patients, the rate of infection was 163.7 per 100 patient-years. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg RoActemra (12.2 per 100 patient years) compared to patients weighing (insert more than or equal sign) 30kg, treated with 8 mg/kg RoActemra (4.0 per 100 patient years).

Infusion reactions[1]

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. Following 184.4 patient-years of exposure with RoActemra in pJIA patients, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and those within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients. No clinically significant hypersensitivity reactions requiring treatment discontinuation were reported during the clinical programme.

Immunogenicity[1]

One patient in the 10 mg/kg <30 kg group developed positive anti-RoActemra antibodies without developing a hypersensitivity reaction, and subsequently withdrew from the study.

Neutrophils[1]

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, a decrease in neutrophil count below 1 x 10^9/l occurred in 3.7% of patients.

Platelets[1]

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, 1% of patients had a decrease in platelet count to ≤50 x 10^3/µl without associated bleeding events.

Hepatic transaminase elevations[1]

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, elevation in ALT or AST ≥3 x ULN occurred in 3.7% and <1% of patients, respectively.

Lipid parameters[1]

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, the highest post-baseline value for cholesterol was >1.5–2 x ULN in one patient (0.5%) and for LDL was >1.5–2 in one patient (0.5%).

Drug interactions[1]

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg RoActemra with 10 to 25 mg MTX once weekly had no clinically significant effect on MTX exposure.

There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents.

Interactions with CYP450 substrates[1]

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as RoActemra, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. RoActemra normalises expression of these enzymes.

When starting or stopping therapy with RoActemra, patients taking medicinal products which are individually adjusted and are metabolised via CYP450, CYP3A4, CYP1A2 or CYP2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin or benzodiazepines) should be monitored as doses may need to be modified to maintain therapeutic effect. Given its long elimination half-life ($t^{1/2}$), the effect of RoActemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Use in specific populations

Paediatric patients[1]

The safety and efficacy of RoActemra in children below 2 years of age has not been established and therefore RoActemra is not recommended for use in these patients.

Renal impairment[1]

No dose adjustment is required in patients with mild renal impairment. RoActemra has not been studied in patients with moderate to severe renal impairment. Renal function should be closely monitored in these patients.

Hepatic impairment[1]

RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

Pregnancy[1]

There are no adequate data from the use of RoActemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk for humans is unknown. Female patients of childbearing potential must use effective contraception during and up to 3 months after treatment.

RoActemra should not be used during pregnancy unless clearly necessary.

Breastfeeding[1]

It is unknown whether RoActemra is excreted in human breast milk. The excretion of RoActemra in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breastfeeding to the child and the benefit of RoActemra therapy to the patient.

Fertility[1]

Available non-clinical RoActemra data do not suggest an effect on fertility.

Dosage and administration

sJIA

The recommended dose of RoActemra in sJIA patients is 8 mg/kg once every 2 weeks in patients weighing ≥30 kg, or 12 mg/kg once every 2 weeks in patients weighing <30 kg. The dose should be calculated based on the patient's body weight at each administration. Please refer to the Step by Step Dosing and Administration Guide for the correct dose. A change in dose should only be based on a consistent change in the patient's body weight over time.[1]

- RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX[1]
- There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA patients. RoActemra is not recommended for use with other biological agents[1]

General dose advice

- Dose interruptions of RoActemra for laboratory abnormalities are recommended[1]
- Reduction of RoActemra dose due to laboratory abnormalities has not been studied in sJIA
  - If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoActemra dosing interrupted until the clinical situation has been evaluated[1]
- The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient[1]

General considerations for administration

RoActemra concentrate for intravenous (IV) infusion should be diluted by a healthcare professional using aseptic technique.[1]

For patients <30 kg

- From a 50 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.6 ml/kg) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml

For patients ≥30 kg

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- Slowly add RoActemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) at 30ºC for 24 hours. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2ºC–8ºC, unless dilution has taken place in controlled and validated aseptic conditions. RoActemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted RoActemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes and must be administered with an infusion set. Do not administer as an IV push or bolus
- RoActemra should not be infused concomitantly in the same IV line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of RoActemra with other medications

pJIA

The recommended dose of RoActemra in pJIA patients is 8 mg/kg once every 4 weeks in patients weighing ≥30 kg, or 10 mg/kg once every 4 weeks in patients weighing <30 kg. The dose should be calculated based on the patient's body weight at each administration. Please refer to the Step by Step Dosing and Administration Guide for the correct dose. A change in dose should only be based on a consistent change in the patient's body weight over time.[1]

- RoActemra can be given as monotherapy (in case of intolerance to MTX or where continued treatment with MTX is inappropriate) or in combination with MTX[1]
- There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for pJIA patients. RoActemra is not recommended for use with other biological agents[1]

General dose advice

- Dose interruptions of RoActemra for laboratory abnormalities are recommended[1]
- Reduction of RoActemra dose due to laboratory abnormalities has not been studied in pJIA
  - If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoActemra dosing interrupted until the clinical situation has been evaluated[1]
- The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient[1]

General considerations for administration

RoActemra concentrate for intravenous (IV) infusion should be diluted by a healthcare professional using aseptic technique.[1]

For patients <30 kg

- From a 50 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.5 ml/kg) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml

For patients ≥30 kg

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- Slowly add RoActemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) at 30ºC for 24 hours. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2–8ºC, unless dilution has taken place in controlled and validated aseptic conditions. RoActemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted RoActemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes and must be administered with an infusion set. Do not administer as an IV push or bolus
- RoActemra should not be infused concomitantly in the same IV line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of RoActemra with other medications

Reference:

1. RoActemra Summary of Product Characteristics. (www.medicines.org.uk/)

If you have any further questions relating to RoActemra please contact Roche Medical Information on +44(0)1707 361010 or email: medinfo.uk@roche.com.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Reporting forms and information can be found at www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44(0)1707 367554.

As RoActemra is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Date of preparation: March 2015 RXUKACTE00047